

On the origin of SARS-CoV-2—The blind watchmaker argument

Chung-I Wu^{1*}, Haijun Wen¹, Jian Lu², Xiao-dong Su², Alice C. Hughes³, Weiwei Zhai⁴, Chen Chen⁵, Hua Chen⁶, Mingkun Li⁶, Shuhui Song⁶, Zhaohui Qian⁷, Qihui Wang⁸, Bingjie Chen¹, Zixiao Guo¹, Yongsun Ruan¹, Xuemei Lu⁹, Fuwen Wei¹⁰, Li Jin¹¹, Le Kang¹², Yongbiao Xue⁶, Guoping Zhao¹³, Ya-Ping Zhang⁹

1. State Key Laboratory of Biocontrol, School of Life Sciences, Sun Yat-sen University, Guangzhou 510275, China;
2. State Key Laboratory of Protein and Plant Gene Research, Center for Bioinformatics, School of Life Sciences, Peking University, Beijing 100871, China;
3. Landscape Ecology Group, Center for Integrative Conservation, Xishuangbanna Tropical Botanical Garden, Chinese Academy of Sciences, Mengla, Mengla, Yunnan 666303, China;
4. Key Laboratory of Zoological Systematics and Evolution, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China;
5. Biomedical innovation center, Beijing Shijitan Hospital, Capital Medical University, Beijing, China.
6. Beijing Institute of Genomics, Chinese Academy of Sciences, and China National Centre for Bioinformation, Beijing 100101, China;
7. Institute of Pathogen Biology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100176, China;
8. CAS Key Laboratory of Pathogen Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences, Beijing 100101, China;
9. State Key Laboratory of Genetic Resources and Evolution, Kunming Institute of Zoology, Chinese Academy of Science, Kunming 650223, China;
10. CAS Key Laboratory of Animal Ecology and Conservation Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China;
11. MOE Key Laboratory of Contemporary Anthropology, Department of Anthropology and Human Genetics, School of Life Sciences, Fudan University, Shanghai 200433, China;
12. State Key Laboratory of Integrated Management of Pest Insects and Rodents, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China;
13. Key Laboratory of Synthetic Biology, Institute of Plant Physiology and Ecology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai 200032, China

*Corresponding author t(wzhongyi@mail.sysu.edu.cn)

In the comparison with SARS-CoV of 2003, SARS-CoV-2 is extremely well adapted to the human populations and its adaptive shift from the animal host to humans must have been even more extensive. By the blind watchmaker argument, such an adaptive shift can only happen prior to the onset of the current pandemic and with the aid of step-by-step selection. In this view, SARS-CoV-2 could not have possibly evolved in an animal market in a big city and even less likely in a laboratory. Discussions of the origin of SARS-CoV-2 need to factor in the long process of adaptive shift and some models have indeed advanced in that direction.

There have been many calls recently for the continued investigations of SARS-CoV-2 origin from both non-academic circles and academia. A recent letter is such an example (Bloom et al., 2021). This Insight piece is a commentary on biological origin based strictly on scientific principles. It is hence not directed toward any particular viewpoint of a non-scientific nature.

There indeed exists a line of arguments that SARS-CoV-2 could not have evolved in nature (Sallard et al., 2021; Segreto and Deigin, 2020), based on genomic features not expected by the authors. Since no known natural law prohibits the SARS-CoV-2 genome to evolve to its current state, the claim of non-natural origin of SARS-CoV-2 is moot. Unless strains that carry the definitive signature of human design (such as barcoding as is commonly done nowadays in tracing cell lineages) can be found, it would be more productive to focus on the natural processes in relation to the SARS-CoV-2 origin.

In this response, we first ask that the meaning of origin be clarified when the call of investigation is made. The origin of any living organisms, be they humans, dogs or flowering plants, is often a prolonged process of evolution with many steps of refinement. Hence, the early evolution usually stretches over an evolutionary time scale and sometimes over a large geographical area. If we treat the origin merely as an event of a particular time and place, there would naturally be disagreements. What then does the origin of SARS-CoV-2 mean? It should be about how, when and where SARS-CoV-2 evolved to become so perfectly adapted to the human conditions. The starting point may be assumed to be a viral strain that is well adapted to some wild animals; hence, there should be an adaptive shift from animal hosts to humans.

The process of adaptive shift is an example of complex evolutionary adaptation that has been cogently argued in Richard Dawkins's popular book "The Blind Watchmaker". In the view of William Paley in 1794 (Paley, 1829), perfect adaptation, akin to an exquisite watch, implies a non-natural process (a creator) that defies the evolutionary theory. This mis-understanding is the crux of Dawkins's Blind Watchmaker argument which prescribes a series of steps, each selecting for some slight improvements from the random assortments of tinkering. Step by step, the culmination of a long series of improvements would emerge as a perfect package (Dawkins, 1996).

The process of adaptive shift should be the central issue of the origin of SARS-CoV-2 but, unfortunately, has been conspicuously neglected. The popular views on the origin of SARS-CoV-2 fall into two categories. The first category is about the possible natural origin. In this view, some wild animals harbor SARS-CoV-2 that are fully adapted to human populations at the time of human-animal contact. This "pre-adaptation" view of perfection via random forces is what Paley objected to in favor of a Creator. Given the rapidity of the spread from December of 2019 on, SARS-CoV-2 appears extremely well adapted to humans in the very beginning of the pandemic. In the second category, SARS-CoV-2 somehow escaped from some virology laboratories (which have multiple identities, depending on the proponents). The escapees are part of legitimate virological experiments of mutagenesis, recombination, genome re-arrangement etc. They accidentally ignited the epidemics after the escape. This is again a pre-adaptation view on a product of perfection at the roll out.

There are several lines of evidence against the pre-adaption view that posits viral adaptation without natural selection. First, there have been numerous studies taking the "rational design" approach to altering viruses in the direction of, for example, immune escape or host range (Bajic et al., 2019; Becker et al., 2008; Menachery et al., 2015). As stated in one of the prominent studies (Menachery et al., 2015), the approach can push the virus in the desired direction but never far enough to drive an epidemic. Second, the results above suggest that adaptation via natural selection would be needed. The evolutionary history of human coronaviruses (OC43, 229E, and NL63) that are associated with the common cold bears this view out. These coronaviruses had shuttled between humans and wild animals for hundreds of years prior to their global spread (Huynh et al., 2012; Normile, 2013). Third, several attempts have been successful in selecting for SARS-CoV-2 strains that can infect mice, which are otherwise resistant to SARS-CoV-2 infection (Dinnon et al., 2020; Gu et al., 2020; Leist et al., 2020). Apparently, the enabling mutations account for such a tiny fraction of mutations that an efficient screening of mutations by natural selection is required. Indeed, in the SARS of 2003-2004 and in COVID-19, the power of natural selection has been amply demonstrated by the increasingly successful new strains (Davies et al., 2021; Korber et al., 2020; Tegally et al., 2020; Voloch et al., 2020) that evolve in humans.

From a non-evolutionary angle, some may argue that the possibility of a fully pre-adapted virus cannot be excluded. This would be analogous to R. Goldschmidt's "Hopeful Monster" view (Goldschmidt, 1982). We wish to point out that, even in this defunct view, an extremely low probability event (i.e., the "hopeful monster") could have happened only over a long evolutionary time span as well as a large geographical region. In contrast, a low probability event of near perfection in the form of SARS-CoV-2 has now been suggested to have happened in a very brief period of time.

In our reasoning, prior to the onset of the COVID-19 pandemic, some forms of multi-step evolution in human populations must be the basis of the extraordinary adaptiveness of SARS-CoV-2. The dilemma is how the evolution could have happened if the final adaptation requires the completion of all steps. In the blind watchmaker argument, each refinement must confer an advantage, however small it is. To address this issue, a model on the incremental evolution of SARS-CoV-2 has been proposed (Ruan et al., 2021). It invokes the arms race between the virus and its animal hosts in a habitat sparsely populated by humans that is referred to as PL0 (the place of origin). The virus subsequently spread to naive human populations which do not have the herd immunity. The place of the first epidemic, referred to as PL1, is not PL0 precisely because the human population in PL1 is immunologically naïve to the virus. This may be true for the "Spanish flu" of 1918 and AIDS as well (Crosby, 2003; Sharp and Hahn, 2011).

In addition to the conceptual arguments, a substantial number of seemingly unconnected reports also point to the possible existence of a PL0 that is distinct from PL1. One such recent report is specific about detecting IgG in samples collected in December of 2019 in the US (Althoff et al., 2021). Others include sporadic occurrences of COVID-19-like cases in the earlier months of 2019 as well as traces of SARS-CoV-2-like materials in the environments in diverse geographical areas (La Rosa et al., 2021; Randazzo et al., 2020). Although such evidence is difficult to evaluate in retrospect, invasions from PL0 must have failed many times before a successful hit at PL1, due to the high stochasticity in the early stage of invasions (Ruan et al., 2020; Ruan et al., 2021). It is also known that diverse coronaviruses exist naturally in bats, and that these families have ranges which stretch over the entire old-world, providing many opportunities for spillover events to occur (Zhou et al., 2021).

The issue of origin is different from many other biological questions because a theoretical model has to precede the experiments. An investigator carrying out the empirical search needs to know what they should be looking for, much like the police need to know what a bank robbery suspect looks like. Even if the model is correct, they may not catch the suspect but a wrong model (and in the case of COVID-19, a blank model) will not lead to the catch. In Ruan et al.'s model (Ruan et al., 2020; Ruan et al., 2021), a seafood market in a large city with the heavy traffic of humans and animals does not have the stability required for the step-by-step adaptive shift in PL0. It is only one possible scenario; nevertheless, those who call for an investigation of the origin should be specific about what the origin means.

The knowledge of the origin of SARS-CoV-2 is important for the simple reason that we have had 3 coronavirus epidemics in the last 2 decades. If there is another one in the next decade, knowing the origin and the subsequent spread (Ruan et al., 2020; Ruan et al., 2021) is the best way to be prepared.

References

- Althoff K.N., Schlueter D.J., Anton-Culver H., Cherry J., Denny J.C., Thomsen I., Karlson E.W., Havers F.P., Cicek M.S., Thibodeau S.N. (2021). Antibodies to SARS-CoV-2 in All of Us Research Program Participants, January 2-March 18, 2020. *Clinical Infectious Diseases*.
- Bajic G., Maron M.J., Adachi Y., Onodera T., McCarthy K.R., McGee C.E., Sempowski G.D., Takahashi Y., Kelsoe G., Kuraoka M., Schmidt A.G. (2019). Influenza Antigen Engineering Focuses Immune Responses to a Subdominant but Broadly Protective Viral Epitope. *Cell Host & Microbe* 25, 827-835.e826.

- Becker M.M., Graham R.L., Donaldson E.F., Rockx B., Sims A.C., Sheahan T., Pickles R.J., Corti D., Johnston R.E., Baric R.S., Denison M.R. (2008). Synthetic recombinant bat SARS-like coronavirus is infectious in cultured cells and in mice. *Proceedings of the National Academy of Sciences* 105, 19944.
- Bloom J.D., Chan Y.A., Baric R.S., Bjorkman P.J., Cobey S., Deverman B.E., Fisman D.N., Gupta R., Iwasaki A., Lipsitch M., Medzhitov R., Neher R.A., Nielsen R., Patterson N., Stearns T., van Nimwegen E., Worobey M., Relman D.A. (2021). Investigate the origins of COVID-19. *Science* 372, 694.
- Crosby A.W. (2003). *America's forgotten pandemic: the influenza of 1918* (Cambridge University Press).
- Davies N.G., Abbott S., Barnard R.C., Jarvis C.I., Kucharski A.J., Munday J.D., Pearson C.A., Russell T.W., Tully D.C., Washburne A.D. (2021). Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. *Science* 372.
- Dawkins R. (1996). *The blind watchmaker: Why the evidence of evolution reveals a universe without design* (WW Norton & Company).
- Dinno K.H., Leist S.R., Schäfer A., Edwards C.E., Martinez D.R., Montgomery S.A., West A., Yount B.L., Hou Y.J., Adams L.E. (2020). A mouse-adapted model of SARS-CoV-2 to test COVID-19 countermeasures. *Nature* 586, 560-566.
- Goldschmidt R. (1982). *The material basis of evolution*, Vol 28 (Yale University Press).
- Gu H., Chen Q., Yang G., He L., Fan H., Deng Y.-Q., Wang Y., Teng Y., Zhao Z., Cui Y., Li Y., Li X.-F., Li J., Zhang N.-N., Yang X., Chen S., Guo Y., Zhao G., Wang X., Luo D.-Y., Wang H., Yang X., Li Y., Han G., He Y., Zhou X., Geng S., Sheng X., Jiang S., Sun S., Qin C.-F., Zhou Y. (2020). Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. *Science* 369, 1603.
- Huynh J., Li S., Yount B., Smith A., Sturges L., Olsen J.C., Nagel J., Johnson J.B., Agnihothram S., Gates J.E. (2012). Evidence supporting a zoonotic origin of human coronavirus strain NL63. *Journal of virology* 86, 12816.
- Korber B., Fischer W.M., Gnanakaran S., Yoon H., Theiler J., Abfalterer W., Hengartner N., Giorgi E.E., Bhattacharya T., Foley B. (2020). Tracking changes in SARS-CoV-2 Spike: evidence that D614G increases infectivity of the COVID-19 virus. *Cell* 182, 812-827. e819.
- La Rosa G., Mancini P., Ferraro G.B., Veneri C., Iaconelli M., Bonadonna L., Lucentini L., Suffredini E. (2021). SARS-CoV-2 has been circulating in northern Italy since December 2019: Evidence from environmental monitoring. *Science of the total environment* 750, 141711.
- Leist S.R., Dinno K.H., Schäfer A., Tse L.V., Okuda K., Hou Y.J., West A., Edwards C.E., Sanders W., Fritch E.J., Gully K.L., Scobey T., Brown A.J., Sheahan T.P., Moorman N.J., Boucher R.C., Gralinski L.E., Montgomery S.A., Baric R.S. (2020). A Mouse-Adapted SARS-CoV-2 Induces Acute Lung Injury and Mortality in Standard Laboratory Mice. *Cell* 183, 1070-1085.e1012.
- Menachery V.D., Yount B.L., Jr., Debbink K., Agnihothram S., Gralinski L.E., Plante J.A., Graham R.L., Scobey T., Ge X.Y., Donaldson E.F., Randell S.H., Lanzavecchia A., Marasco W.A., Shi Z.L., Baric R.S. (2015). A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nat Med* 21, 1508-1513.
- Normile D. (2013). Understanding the Enemy. *Science* 339, 1269.
- Paley W. (1829). *Natural Theology: or, Evidences of the Existence and Attributes of the Deity, Collected from the Appearances of Nature* (Lincoln and Edmands).
- Randazzo W., Truchado P., Cuevas-Ferrando E., Simón P., Allende A., Sánchez G. (2020). SARS-CoV-2 RNA in wastewater anticipated COVID-19 occurrence in a low prevalence area. *Water Research* 181, 115942.
- Ruan Y., Luo Z., Tang X., Li G., Wen H., He X., Lu X., Lu J., Wu C.-I. (2020). On the founder effect in COVID-19 outbreaks – How many infected travelers may have started them all? *National Science Review*.
- Ruan Y., Wen H., He X., Wu C.I. (2021). A theoretical exploration of the origin and early evolution of a pandemic. *Sci Bull (Beijing)* 66, 1022-1029.
- Sallard E., Halloy J., Casane D., Decroly E., van Helden J. (2021). Tracing the origins of SARS-COV-2 in coronavirus phylogenies: a review. *Environmental Chemistry Letters*, 1-17.

Segreto R., Deigin Y. (2020). The genetic structure of SARS - CoV - 2 does not rule out a laboratory origin: SARS - COV - 2 chimeric structure and furin cleavage site might be the result of genetic manipulation. *BioEssays*, 2000240.

Sharp P.M., Hahn B.H. (2011). Origins of HIV and the AIDS pandemic. *Cold Spring Harbor perspectives in medicine* 1, a006841.

Tegally H., Wilkinson E., Giovanetti M., Iranzadeh A., Fonseca V., Giandhari J., Doolabh D., Pillay S., San E.J., Msomi N. (2020). Emergence and rapid spread of a new severe acute respiratory syndrome-

related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. *medRxiv*.

Voloch C.M., Silva F R.d., de Almeida L.G.P., Cardoso C.C., Brustolini O.J., Gerber A.L., Guimarães A.P.d.C., Mariani D., Costa R.M.d., Ferreira O.C., Cavalcanti A.C., Frauches T.S., de Mello C.M.B., Galliez R.M., Faffe D.S., Castiñeiras T.M.P.P., Tanuri A., de Vasconcelos A.T.R. (2020). Genomic characterization of a novel SARS-CoV-2 lineage from Rio de Janeiro, Brazil. *medRxiv*, 2020.2012.2023.20248598.

Zhou H., Ji J., Chen X., Bi Y., Li J., Wang Q., Hu T., Song H., Zhao R., Chen Y. (2021). Identification of novel bat coronaviruses sheds light on the evolutionary origins of SARS-CoV-2 and related viruses. *Cell*.